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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,821	01/16/2007	August Verbruggen	50304/021002	7212

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EXAMINER	
ARIANI, KADE	
ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
03/04/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/595,821	VERBRUGGEN ET AL.	
	Examiner	Art Unit	
	Kade Ariani	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-27,30,31,35,37-40 and 43-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-27,30,31,35,37-40 and 43-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed on December 03, 2009, has been received and entered.

Claims 28, 29, 32-34, 36, 41, and 42 have been canceled.

New claims 43-49 have been added.

Claims 23-27, 30, 31, 35, 37-40, and 43-49 are pending in this application and were examined on their merits.

Applicant's arguments with respect to claims 23-27, 30, 31, 35, 37-40, and 43-49 filed on 12/03/2009 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claim 27 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn due to Applicant's amendments to the claims filed on 12/03/2009.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kavalkovich et al. (In vitro Cell. Dev. Biol. - Animal, 2002, Vol. 38, p.457-466) in view of Ronghua et al. (Carbohydrate Polymers, April 2003, Vol. 52, p.19-24) and further in view of Kawada et al. (Arch Dermatol Res, 1999, Vol. 291, p.542-547) and further in view of Rihova B. (Advanced Drug Delivery Reviews, 1996, Vol. 21, p.157-176), is withdrawn due to Applicant's amendments to the claims filed on 12/03/2009.

Claims 23-27, 30, 31, 35, 37-40, and 43-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Verbruggen et al. (J Rheumatol., 1999, Vol. 26 , p.1663-1671) and Hauselmann et al. (American Journal of physiology, 1996, Vol. 271, p.C742-C752) in view of Rosenberg et al. (US 2003/0161884 A1) and further in view of Kavalkovich et al. (In vitro Cell. Dev. Biol. - Animal, 2002, Vol. 38, p.457-466) and of Ronghua et al. (Carbohydrate Polymers, April 2003, Vol. 52, p.19-24) and of Kawada et al. (Arch Dermatol Res, 1999, Vol. 291, p.542-547) and of Rihova B. (Advanced Drug Delivery Reviews, 1996, Vol. 21, p.157-176).

Claims 23-27, 30, and 43 are drawn to an *in vitro* method for the cultivation of chondrogenic cells, comprising the step of contacting said cells with a matrix comprising

1 to 10 µg/ml polysulphated alginate, the matrix is suitable for the implantation into a human body, the matrix is further comprises nutrient media, the matrix is further comprises unsulphated alginate, polysulphated alginate and alginate are present in a weight ratio of between 1:1000 and 1:10,000, said chondrogenic cells are chondrocyte precursor cells, and chondrogenic cells are chondrocytes.

Claims 31, 35, 37, 38 and 44-47 are drawn to a matrix comprising 1 to 10 µg/ml polysulphated alginate and chondrogenic cells, the matrix further comprises nutrient medium, the matrix further comprises unsulphated alginate, chondrocyte precursor cells, and chondrocytes.

Claims 39, 40, 48, and 49 are drawn to a method for the treatment of a cartilage defect comprising administering to the cartilage defect a matrix comprising polysulphated alginate, the matrix further comprises chondrogenic cells.

Verbruggen et al. teach an *in vitro* method for the cultivation of chondrocytes, comprising the step of contacting chondrocytes (chondrogenic cells) with 10 µg/ml polysulphated polysaccharides, chondroitin polysulfate and xylosan polysulfate (Abstract). Verbruggen et al. teach large aggregates of aggrecans reflects the capability of chondrocytes to restore extracellular matrix of articular cartilage *in vitro*, polysulphated polysaccharides (chondroitin and xylosan polysulfates) significantly increased the synthesis rate and accumulation of the aggrecan in aggregates in the extracellular environment *in vitro* (Abstract). It must be noted that aggrecan molecules residing in the articular cartilage matrix are more susceptible to degradation by proteolytic enzymes (see Hauselmann et al. Abstract). Verbruggen et al. further teach

culturing cells in an artificial matrix (gelled agarose) in the presence of a nutrient medium (polysulphated polysaccharides used at 10 µg/ml of culture medium) (p. 1664 1st column Materials & Methods" 3rd & 4th paragraphs, p. 1665 1st column 4th paragraph line 7, p.1666 1st column last paragraph lines 2-3, and p.1668 Discussion 1st paragraph lines 1-4). Verbruggen et al. teach sulfated polysaccharides show repair-promoting effects and sulfated polysaccharides that positively affect cartilage metabolism could be classified among the structure modifying osteoarthritis drugs and offer therapeutic benefits in the management of osteoarthritis (OA) (treatment of a cartilage defect) (p.1670 1st column 2nd paragraph lines 10-11, and 3rd paragraph lines 6-10).

Verbruggen et al. do not teach polysulphated alginate, unsulphated alginate, polysulphated alginate and alginate are present in a weight ratio of between 1:1000 and 1:10,000, chondrocyte precursor cells, and administering to the cartilage defect a matrix comprising polysulphated alginate. However, Rosenberg et al. teach polysulphated alginate (polysulfates prepared from alginic acid) and chondroitin polysulphated are heparinoids and have heparin-like effect, i.e. inhibit the coagulation of blood (see p.2 2nd column paragraph 0021). Therefore, at the time the invention was made a person of ordinary skill in the art would recognize the interchangeability of polysulphated alginate and chondroitin polysulphated, since they are both polysulphated polysaccharides with heparin-like effect.

Moreover, Kavalkovich et al. teach to an *in vitro* cultivation of human mesenchymal stem cells are source of chondrocyte precursor cells when cultured in a matrix (three-dimensional format) comprising unsulphated alginate (2.4% sodium

alginate, an alginate layer culture system) (Abstract, p.457 2nd column end paragraph lines 1-4, 2nd paragraph Lines 2-3 and 14-15). Kavalkovich et al. teach culture of cells within the alginate results in a more uniform and substantially enhanced chondrogenic responses (p.462 2nd column "Discussion" 1st paragraph lines 16-18). Kavalkovich et al. teach because cartilage has poor regenerative capacity, cell therapy is an attractive option either for retarding degenerative changes in the case of osteoarthritis of for restoring functional tissue after traumatic injury (p.464 1st column end paragraph lines 1-4).

Furthermore, Ronghua et al. teach alginate sulfates (AS) has anticoagulant activity (Abstract and Introduction 2nd column end paragraph lines 1-6, and p.20 Scheme 1.). Ronghua et al. teach alginate sulfates showed anticoagulant activity (APTT) in a dose dependent manner, as 226 s at about 17 μg/ml (p.23 1st column 2nd paragraph line 6-7, and Figure 3.). It must be noted that a person of ordinary skill in the art at the time the invention was made would have realized that thrombogenicity is one of the discriminating factor between compatible and non-compatible materials, and a matrix suitable for implantation, must be non-thrombogenic (anticoagulant activity) to be biocompatible (see Rihova, p.163 1st column 2.3.2. 7-10).

Further motivation to use unsulphated alginate is in Kawada et al. who teach unsulphated alginate (alginate with no sulfate group) at the concentration 1 μg/ml stimulated endothelial cell migration and proliferation (Abstract and p.546 1st column 2nd paragraph lines 17-19, and 3rd paragraph lines 8-14). It must be noted that a person of ordinary skill in the art at the time the invention was made would have realized that

stimulation of endothelial cell migration and proliferation were necessary for vascularization of the implant.

Therefore, a person of ordinary skill in the art at the time the invention was made, knowing the positive affect of sulfated polysaccharides like chondroitin polysulphate on cartilage metabolism and its repair-promoting effects and anticoagulant activity, would have been motivated to substitute polysulphated alginate for chondroitin polysulphate in the method and matrix composition as taught by Verbruggen et al. according to the teachings of Rosenberg et al. and Ronghua et al. with a reasonable expectation of success in order to provide an *in vitro* method for the cultivation of chondrogenic cells and a matrix comprising polysulphated alginate (1 to 10 µg/ml) and chondrogenic cells, a pharmaceutical composition comprising the matrix, and a method for the treatment of cartilage defect, because a person of ordinary skill in the art at the time the invention was made would have recognized the interchangeability of polysulphated alginate and chondroitin polysulphated.

Moreover, a person of ordinary skill in the art at the time the invention was made, would have been motivated to modify the method as matrix composition as taught by Verbruggen et al. by using unsulphated alginate and chondrocyte precursor cells according to the teachings of Kavalkovich et al. with a reasonable expectation of success in providing an *in vitro* method for the cultivation of chondrogenic cells and a matrix comprising unsulphated alginate and chondrocyte precursor cells. Because Kavalkovich et al. teach culture of cells within the unsulphated alginate results in a more uniform and substantially enhanced chondrogenic responses and because Kawada et

al. teach unsulphated alginate (alginate with no sulfate group) at the concentration 1 µg/ml stimulated endothelial cell migration and proliferation.

Accordingly, a person of ordinary skill in the art at the time the invention was made knowing that Ronghua et al. teach alginate sulfates showed anticoagulant activity at about 17 µg/ml, Verbruggen et al. teach polysulphated polysaccharides used 10 µg/ml of culture medium, and Kawada et al. teach unsulphated alginate at the concentration 1 µg/ml stimulated endothelial cell migration and proliferation, would have been motivated to optimize the weight ratio of the polysulphated alginate to unsulphated alginate to be used in the method as taught by Verbruggen et al. by routine experimentation.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kade Ariani whose telephone number is (571) 272-6083. The examiner can normally be reached on IFP.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kade Ariani
Examiner
Art Unit 1651

/Leon B Lankford/
Primary Examiner, Art Unit 1651